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10/675,172	09/29/2003	Stephen Donovan	17510DIV2 (BOT)	5916

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EXAMINER	
FORD, VANESSA L	
ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/675,172	DONOVAN, STEPHEN	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-28,36 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-28, 36 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

1. This Office Action is responsive to Applicant's amendment and response filed August 3, 2007. Claims 22, 25 and 37 have been amended. Claims 1-21 and 29-35 have been cancelled. Claims 22-28 and 36-37 are under examination.

Rejections Withdrawn

2. In view of Applicant's amendment and response the following objection/rejections have been withdrawn:

a) objection of claim 37 has been withdrawn, page 3, paragraph 4 of the previous Office action.

b) rejection of claim 25 under 35 U.S. second paragraph has been withdrawn.

c) rejection of claims 22-23, 26-28 and 36 under 35 U.S.C. 102(e), pages 3-5, paragraph 6 of the previous Office action.

d) rejection of claims 25 and 37 under 35 U.S.C. 103(a), pages 5-7 paragraph 7 of the previous Office action.

e) rejection of claims 22-28 and 36-37under 35 U.S.C. 103(a), pages 8-10 paragraph 8 of the previous Office action.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 22-28 and 36-37 are rejected under 35 U.S.C. 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claim 22 recite in step (d)"solubilizing the botulinum toxin provided in the dry state with the fluid, wherein solubilization of the pharmaceutical composition permits diffusion". Claim 22, step c (i) recites a pharmaceutical composition comprising a botulinum toxin and an enhancing agent. It is unclear what is being solubilized in step (d), only the botulinum toxin or the botulinum toxin and the enhancing agent? Clarification and/or correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 22, 28 and 36 are rejected under 35 U.S.C. 103(a) as unpatentable over Graham *(U.S. Patent No. 6,939,852 B2 published September 6, 2005)* in view of Mohr et al *(U.S. Patent No. 5,591,767 published January 7, 1997).*

Independent claim 22 is drawn to a method of reducing neurotransmitter release in a subdermal structure of a patient, the method comprising the steps of: (a) non-chemically disrupting the stratum corneum of the patient's skin to reduce impermeability of the stratum corneum and (b) applying a fluid to the patient's skin, (c) applying a transdermal patch to the skin of a patient in an area that had the stratum corneum disrupted in step (a), the transdermal patch comprising; i) a pharmaceutical composition comprising a stabilized botulinum toxin provided in a dried state and an enhancing agent that is mixable with the stabilized botulinum toxin provided in a dried state and facilitates transdermal administration of a botulinum toxin in a bioactive form to a subdermal target site of a human patient without being administered to the patient's circulatory system; and ii) an adhesive layer disposed to one side of the transdermal patch to removably secure the patch on the patient's skin; when the pharmaceutical composition is incorporated into the adhesive layer; and (d) solubilizing the botulinum toxin provided in the dry state with the fluid, wherein solubilization of the pharmaceutical composition permits diffusion of the pharmaceutical composition from the adhesive layer into the patient's skin thereby reducing neurotransmitter release in a subdermal structure.

Graham teaches a pharmaceutical composition comprising botulinum toxin A incorporated into a polymetric matrix of a suitable carrier and formed into a adhesive

patch for use in conjunction with a skin permeation enhancer such as DMS or Azone (column 4). Graham teaches that the botulinum toxin used in the invention is dried or lyophilized (column 4).

Graham does not teach the claim limitation "wherein the pharmaceutical composition is incorporated into the adhesive layer" and "solubilizing the botulinum toxin in the dry state with the fluid, wherein solubilization of the pharmaceutical composition permits diffusion of the pharmaceutical composition from the adhesive layer into the patient's skin thereby reducing neurotransmitter release in a subdermal structure".

Mohr et al teach transdermal patches that are adhesive matrix patches where the drug and the enhancer are formulated into the skin adhesive layer (column 7). Mohr et al teach that the adhesive layer serves both as the enhancer reservoir as well as the adhesive layer which attaches the patch to the patient's skin (column 7).

It would have been *prima facie* obvious at the time the invention was made to modify the transdermal patch as taught by Graham to include the incorporation of the drug (e.g. botulinum toxin and the enhancer) into the adhesive layer according to Mohr et al because Mohr et al has demonstrated that this design of transdermal patch is simple but effective in delivering drugs to the skin. It would be expected, absent evidence to the contrary, that a transdermal patch comprising botulinum toxin and an enhancer within the adhesive layer would be an effective way to facilitate the delivery of active agents such as botulinum toxin to a subdermal target of a patient.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one product, and a person of

ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". Thus, it would be obvious to combine the transdermal patch comprising botulinum toxin and an enhancer as taught by Graham and the transdermal patch (drug or enhancer or enhancing agent in adhesive layer) as taught by Mohr et al because *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that it is obvious to use a known technique to improve a known product that is ready for improvement to yield predictable results.

5. Claims 23-24 are rejected under 35 U.S.C. 103(a) as unpatentable over Graham and Mohr et al as applied to claims 22, 28 and 36 and in further in view of Smith *(U.S. Patent 5,587, 396 published December 24, 1996).*

Dependent claims 23-24 are drawn to "the method of claim 22, wherein the stratum corneum is disrupted by abrasively removing the stratum corneum" and "wherein the stratum corneum is disrupted by applying an adhesive material to the patient's skin and removing the adhesive material applied thereto".

Graham and Mohr et al have been described previously.

Graham and Mohr et al do not teach the dependent claim limitations "wherein the stratum corneum is disrupted by abrasively removing the stratum corneum" and

"wherein the stratum corneum is disrupted by applying an adhesive material to the patient's skin and removing the adhesive material applied thereto".

Smith teaches that tape stripping is an effective barrier disruption method (column 16). Smith teaches that tape stripping vary widely with different individuals (column 16).

It would have been *prima facie* obvious at the time the invention was made to abrasively disrupt the stratum corneum by tape stripping because Smith teaches that tape stripping is an effective barrier disruption method. It would be expected barring evidence to the contrary, that the use of tape stripping would be effective in increasing the permeability of the human skin and thereby facilitating drug delivery.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one product, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". Thus, it would be obvious to combine the transdermal patch comprising botulinum toxin and an enhancer as taught by Graham, the incorporation of a drug and enhancing agent within the adhesive layer of a transdermal patch as taught by Mohr et al and the tape stripping method as taught by Smith et al because KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727,

1741 (2007), disclosed that it is obvious to use a known technique to improve a known product that is ready for improvement to yield predictable results.

6. Claims 25 and 37 are rejected under 35 U.S.C. 103(a) as unpatentable over Graham, Mohr et al, Smith et al as applied to claims 22-24, 28 and 36 and in further view of Mitragotri et al *(Science, Vol. 269, August 11, 1995).*

Dependent claims 25 and 37 are drawn to "the method of claim 22, wherein the stratum corneum is disrupted by applying ultrasound at a frequency between 20 kHz to 1 MHz at an intensity that does not permanently damage the patient's skin" and "wherein the ultrasound application is delivered prior to application of the botulinum toxin to the skin".

Graham, Mohr et al, Smith et al have been described previously.

Graham, Mohr et al, Smith et al do not teach dependent claim limitations "the method of claim 22, wherein the stratum corneum is disrupted by applying ultrasound at a frequency between 20 kHz to 1 MHz" and "wherein the ultrasound application is delivered prior to application of the botulinum toxin to the skin".

Mitragotri et al teach a method of applying ultrasound to promote delivering therapeutic doses of proteins across the skin of a patient (see the Abstract). Mitragotri et al teach that the ultrasound is used at a low frequency of about 20 KHz (see p. 850, 3rd col). Mitragotri et al teach that ultrasound can promote transdermal delivery of high molecular weight proteins (page 850).

It would have been *prima facie* obvious at the time the invention was made to modify the transdermal patch as taught by Graham, Mohr et al and Smith et al combined above because Graham teaches that can effectively deliver botulinum toxin to a patient's skin, Mohr et al has demonstrated the design of their transdermal patch is simple, yet effective at delivering drugs to the skin and Mitragotri et al teach a method of applying ultrasound to promote delivery of therapeutic doses of proteins across the skin of a patient. It would be expected, absent evidence to the contrary, that ultrasound applied to a patient's skin according to Mitragotri et al would enhance the delivery of the pharmaceutical compositions (e.g. botulinum toxin and an enhancer) incorporated within the adhesive layer of the transdermal patch (as taught by the combination of Graham and Mohr et al) into the subdermal layers of a patient's skin.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one product, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". Thus, it would be obvious to combine the transdermal patch comprising botulinum toxin and an enhancer as taught by Graham, the incorporation of a drug and enhancing agent within the adhesive layer of a transdermal patch as taught by Mohr et al , the tape stripping method as taught by Smith et al and the technique of ultrasound as taught by Mitragotri et al because KSR

International Co. v. Teleflex Inc., 127 S. Ct. 1727, 1741 (2007), disclosed that it is obvious to use a known technique to improve a known product that is ready for improvement to yield predictable results.

7. Claims 26-27 are rejected under 35 U.S.C. 103(a) as unpatentable over Graham, Mohr et al, Smith et al, Mitragotri et al as applied to claims 22-25, 28 and 36-37 and in further view of Yuzhakov et al *(U.S. Patent No. 6,565, 532 B1 published May 20, 2003)*.

Dependent claims 26-27 are drawn to "the method of 22 wherein the stratum corneum is disrupted by passing an electrical current from a first point on the patient's skin to a second point on the patient's skin" and "wherein the electrical current is passed to create a plurality of pores in the stratum corneum to enhance passage of botulinum toxin the subdermal structures".

Graham, Mohr et al, Smith et al and Mitragotri et al have been described previously.

Graham, Mohr et al, Smith et al and Mitragotri et al do not teach dependent claim limitations "wherein the stratum corneum is disrupted by passing an electrical current from a first point on the patient's skin to a second point on the patient's skin" and "wherein the electrical current is passed to create a plurality of pores in the stratum corneum to enhance passage of botulinum toxin the subdermal structures".

Yuzhakov et al teach that the drug delivery portion of this invention uses the microneedle array to provide electrodes that apply electric potential

between electrodes and one of the electrodes is filled with an ionized drug and the charged drug molecules move into the body to the applied electric potential. Therefore, the claim limitation "wherein the stratum corneum is disrupted by passing electrical current from a first point on the patient's skin to a second point on the patient's skin" and "wherein the electrical current is passed to create a plurality of pores in the stratum corneum to enhance passage of botulinum toxin the subdermal structures".

taught in the prior art reference. Yuzhakov et al teach a method of reducing neurotransmitter release in a subdermal structure of a patient by dispensing a fluid into the skin comprising providing a microneedle array structure (Abstract and claim 20, column 56). Yuzhakov et al teach that the microneedle array may be contained in a transdermal patch (columns 3-4). Yuzhakov et al teach that botulinum toxin can be delivery through the microneedle array. Yuzhakov et al teach a transdermal patch (columns 3-4) comprising a pharmaceutical composition which comprises a botulinum (column 51, lines 56-63) and an enhancing agent (polymers) (column 28). Yuzhakov et al teach that ultrasound may be used to increase transdermal flow rate when used with microneedle arrays of the invention (column 5).

It would have been *prima facie* obvious at the time the invention was made to use the electrodes as taught by Yuzhakov et al in the method of reducing neurotransmitter release in a subdermal structure of a patient because Yuzhakov et al teach a method of reducing neurotransmitter release in a subdermal structure of a patient by dispensing a fluid into the skin providing a microneedle array structure comprising electrodes. It

would be expected, absent evidence to the contrary, that using the microneedle array comprising electrodes that apply electric potential to a patients skin as taught by Yuzhakov et al and the ultrasound applied to a patient's skin according to Mitragotri et al would enhance the delivery of the pharmaceutical compositions (e.g. botulinum toxin and an enhancer) incorporated within the adhesive layer of the transdermal patch (as taught by the combination of Graham and Mohr et al) into the subdermal layers of a patient's skin.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one product, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". Thus, it would be obvious to combine the transdermal patch comprising botulinum toxin and an enhancer as taught by Graham, the incorporation of a drug and enhancing agent within the adhesive layer of a transdermal patch as taught by Mohr et al , the tape stripping method as taught by Smith et al, the technique of ultrasound as taught by Mitragotri et al and the microneedle array to provide electrodes that apply electric potential to the patient's skin as taught by Yuzhakov et al because KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727, 1741 (2007), disclosed that it is obvious to use a known technique to improve a known product that is ready for improvement to yield predictable results.

Status of Claims

8. No claims allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vanessa L. Ford whose telephone number is (571) 272-0857. The examiner can normally be reached on 9 am- 6 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Biotechnology Patent Examiner
October 31, 2007

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